

**FAST FACTS AND CONCEPTS #75
METHADONE FOR THE TREATMENT OF PAIN**

Gail Gazelle MD and Perry G Fine MD

Introduction Methadone, a potent opioid agonist, has many characteristics that make it useful for the treatment of pain when continuous opioid analgesia is indicated. Although available for decades, its use has gained renewed interest due to its low cost, inactive metabolites, and many routes of administration. This *Fast Fact* will introduce methadone's pharmacology and clinical use as an analgesic.

Pharmacology Unlike morphine, methadone is a racemic mix; one stereoisomer acts as a NMDA receptor antagonist, the other is a mu-opioid receptor agonist. The NMDA mechanism plays an important role in the prevention of opioid tolerance, potentiation of opioid effects, and is the theoretical basis for its use in neuropathic pain syndromes, although this latter impression is largely anecdotal.

Methadone is highly lipophilic with rapid GI absorption and onset of action. It has a large initial volume of distribution with slow tissue release. Oral bioavailability is high, ~ 80%. Unlike morphine there are no active metabolites and biotransformation to an active drug is not required. The major route of metabolism is hepatic with significant fecal excretion; renal excretion can be enhanced by urine acidification (pH <6.0). Unlike morphine, no dose adjustment is needed in patients with renal failure since there are no active metabolites.

Prescribing Methadone is available in tablet, liquid and injectable forms; oral preparations can be used rectally. Parenteral routes include IV bolus dosing or continuous infusion. Any clinician with a Schedule II DEA license can prescribe methadone for pain; a special license is only required to prescribe methadone for the treatment of addiction. In some jurisdictions, it is necessary to apply the words "for pain" on the prescription.

Cautions Unlike morphine, hydromorphone, or oxycodone, methadone has an extended terminal half-life of up to 190 hours. This half-life does not match the observed duration of analgesia (6-12 hours) after steady state is reached. This long half-life can lead to increased risk for sedation and respiratory depression, especially in the elderly or with rapid dose adjustments. *Rapid titration guidelines for other opioids do not apply to methadone.* Given recent reports that high-dose methadone may be associated with development of QT interval prolongation and Torsades de Pointes, EKG monitoring may be appropriate when changes in dosage are made (depending upon life expectancy and goals of care).

Pediatrics With close monitoring by an experienced prescriber, methadone has been used safely in children, although the safety, effectiveness, and the pharmacokinetics of methadone in patients below the age of 18 years have not been established by the Food and Drug Administration.

Potency An important property of methadone is that its apparent potency, compared to other opioids, varies with the patient's current exposure to other opioids. See below for a suggested dosing guide for opioid tolerant patients (Reference 1).

<u>Daily oral morphine dose equivalents</u>	<u>Conversion ratio of oral morphine to oral methadone</u>
<100 mg	3:1 (i.e. 3 mg morphine = 1 mg methadone)
101-300 mg	5:1
301-600 mg	10:1
601-800 mg	12:1
801-1000 mg	15:1
>1001 mg	20:1

Due to incomplete cross-tolerance, it is recommended that the initial dose is 50-75% of the equianalgesic dose.

Key Points

- Compared to morphine, methadone is inexpensive, safe in renal failure, will provide a longer duration of action, and has a theoretic advantage in neuropathic pain, although the latter point has not been reliably demonstrated.
- Because of its long and variable elimination half-life methadone is not an ideal opioid when rapid dose adjustments are needed; do not increase oral methadone more frequently than every 4 days.
- Dose conversion to:from other opioids and methadone is complex and particularly more dangerous than other opioids; consultation with pain or palliative specialists familiar with methadone use is recommended.
- Patient and family education is essential as they may misinterpret prescription of methadone to mean that their physician believes that they are an addict.

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Version History: This *Fast Fact* was originally edited by David E Weissman MD. 2nd Edition published July 2006; 3rd Edition June 2015. Current version re-copy-edited April 2009; then re-copy-edited again by Sam Maiser MD on June 2015 -- additional references were included, the pediatric section was added, and clarification about the role of methadone in neuropathic pain was included.

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